Once we can say that there are differences between people that are easily demonstrable at the genetic level, then society will have to come to grips with understanding diversity—and we are not prepared for that.
David Baltimore, U.S. microbiologist (1983)

AGRICULTURE

Rice and Rice Blast: New Bases for Comparison

In a landmark year for agricultural genomics, the sequences of two types of rice, *Oryza sativa* ssp. *indica* and *O. sativa* ssp. *japonica*, were reported in the 5 April 2002 issue of *Science*. Then, on 17 July 2002, came the announcement from the National Science Foundation that the complete genome of *Magnaporthe grisea*, the fungus that causes rice blast disease, had also been sequenced. With the complete genome sequence of both a host and a pathogen, scientists now have the necessary tools to dissect the weapons of the invader along with the defense mechanisms employed by the host crop to withstand attack.

Rice, which feeds half the world's population, was selected for sequencing because it has the shortest genome of the economically important grains. Data gleaned from sequencing the rice genome can be applied to other crops—a boon to companies (such as Monsanto and the Swiss agrochemical company Syngenta) that are interested in developing transgenic crops. Rice blast, which can cause up to 20% loss in grain yield each year, was selected because it is typical of the many fungal pathogens that attack plants; more than 80% of all plant diseases are caused by fungi. "Although these sequences are specific to the rice and rice blast genomes, they will provide a model system for understanding host–pathogen interactions in other cereals and staple food crops," says Ralph Dean, director of the North Carolina State University Fungal Genomics Laboratory and leader of the group that sequenced the *M. grisea* genome.

A consortium of Chinese scientists led by the Beijing Genomics Institute reported the sequence for *indica*, the type of rice widely grown in China and southern Asia, while Syngenta carried out the sequencing of *japonica*, the type grown in Japan and northern Asia. All three groups used the whole-genome shotgun sequencing method, which decodes multiple short fragments of DNA. The many small pieces must then be assembled in proper order and located to their respective chromosomes using bioinformatics computer programs to predict the location of genes on the chromosomes.

But predictions based on computer algorithms are not always accurate, says Daniel Ebbole, an associate professor of plant pathology and microbiology at Texas A&M University. To test the accuracy of the bioinformatics-generated predictions, his lab is sequencing expressed rice and rice blast genes that are known to produce proteins. He is starting with expressed sequences from RNA isolated from the organism, which is translated into the organism's DNA sequence without the intervening unexpressed sequences that are generated in the shotgun sequencing method. Because RNA degrades rapidly, it is not practical to sequence whole genomes using this approach, but it is essential for validating the accuracy of the sequences derived from the shotgun approach.

Whereas the Chinese made the *indica* sequence freely available to the public (**http://rgp.dna.affrc.go.jp/cgi-bin/statusdb/seqcollab.pl**), access to the *japonica* database is restricted because Syngenta wanted to protect its commercialization exclusivity and patent rights. This has sparked an outcry from scientists in the public sector who feel there should be no restrictions on data that are published in a scientific journal.

However, much of the *japonica* sequence will be publicly available soon. The International Rice Genome Sequencing Project, a 10-nation consortium, is also sequencing the *japonica* genome using bacterial artificial chromosome libraries, a more time-consuming but also more accurate approach. These libraries contain DNA pieces from each of the organism's chromosomes and so allow the assignment of sequences to their chromosomes. This, in turn, facilitates proper alignment of the sequence data. Project coordinators hope that by the end of 2002, some 95% of the *japonica* sequence will be available on the public NIH-administered database GenBank (**http://www.ncbi.nlm.nih.gov/Genbank/**).

Breakthroughs in genomics could eventually lead to long-term benefits to human health and the environment, including new strategies for reducing the use of fungicides and the creation of new chemicals that are more precise and less toxic. Rice could be bioengineered to augment its defense system for warding off invasion. The genomic data could also enhance marker-assisted selection for conventional breeding and spark genetic engineering strategies to address otherwise intractable problems.

In the meantime, there are several safe and effective alternatives for fighting rice blast, including planting early in the growing season, use of resistant rice varieties, avoiding excessive nitrogen fertilizer use, and proper flooding of rice paddies. A project sponsored by the Manila, Philippines–based International Rice Research Institute and begun in 1997 involved planting mixtures of glutinous and nonglutinous rice in the same fields, which virtually eliminated rice blast in Yunnan province and other parts of China. **–Mary Eubanks**

Blasting through a breakthrough. The sequencing of the genomes for rice and rice blast (inset) offers scientists an unprecedented opportunity to compare a host and pathogen, and possibly the means of creating more pest-resistant plants.

PhotoDisc; inset: Richard J. Howard/DuPont Crop Genetics

ENVIRONMENTAL DISEASE

Smoking Inflames Joints

After years of researching the effects that cigarette smoking has on rheumatoid arthritis, Derek Mattey has some advice, especially for women: Don't start smoking! In his most recent research, Mattey, a senior scientist at the Staffordshire Rheumatology Centre in Stoke-on-Trent, England, determined that if a woman has ever smoked cigarettes, even if she has since quit, she is more likely to have a more severe form of rheumatoid arthritis than women who have never smoked. This is especially true if she, like millions of other people, lacks a key gene.

Pointing the finger. New data confirm that smoking has a hand in the development of severe rheumatoid arthritis in women.

"This is an important study," says John Klippel, medical director of the Atlanta, Georgia–based Arthritis Foundation. "It confirms that cigarette smoking plays a role in rheumatoid arthritis." Klippel says the suggestion of a genetic role in the severity of rheumatoid arthritis also makes Mattey's work important for understanding how the disease begins and progresses.

Mattey and his colleagues, reporting in the March 2002 issue of *Arthritis & Rheumatism*, say that the reason why smoking increases the severity of the disease appears to hinge on the relationship between smoking, rheumatoid arthritis, and glutathione *S*-transferase M1 (GSTM1). This enzyme helps convert environmental toxicants, such as those found in cigarette smoke, to less toxic, more hydrophilic products that can be more easily metabolized and excreted. About half of all people lack the *GSTM1* gene, Mattey says, making it a very common polymorphism. But the bad news for women smokers is that lacking the *GSTM1* gene and having rheumatoid arthritis combines for a more debilitating course of the disease.

The researchers used polymerase chain reaction genotyping to determine who among 164 women with rheumatoid arthritis had the *GSTM1* gene. They also tested the women for rheumatoid factor, an immune complex found in the blood and synovial fluid of patients with rheumatoid arthritis. About 80% of patients with rheumatoid arthritis test positive for rheumatoid factor, and the level of rheumatoid factor correlates positively with the severity of the disease. The women underwent radiologic tests to determine the extent of their rheumatoid arthritis damage (their "Larsen score"), and took the Health Assessment Questionnaire to determine how the disease had affected their capacity to perform common activities of daily living.

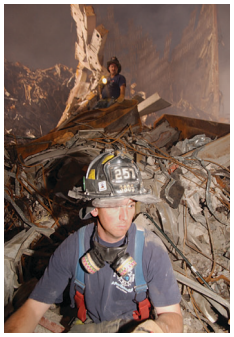
The researchers found that 58.5% of the women did not have the *GSTM1* gene. They also ascertained that 51.3% of the women had never smoked, and 29.9% were current smokers. Women who lacked the *GSTM1* gene and had ever or currently smoked were three times more likely to be rheumatoid factor positive than women who lacked the gene and had never taken up cigarettes. Patients who lacked the *GSTM1* gene and had ever smoked also had significantly higher Larsen and Health Assessment Questionnaire scores than did those who lacked the gene and had never smoked.

"We were able to show that the combination of smoking and lack of the *GSTM1* gene was correlated with a greater likelihood to be rheumatoid factor positive, and the questionnaires and radiology studies confirmed that these same individuals have more advanced, more severe rheumatoid arthritis," Mattey says.

The researchers aren't sure which smoke toxicants are responsible, or how they work. They are now trying to determine if smoking somehow induces the production of rheumatoid factor, and if ambient cigarette smoke also impacts rheumatoid arthritis. "It is difficult to say from this study if second-hand smoke has an effect on the severity of rheumatoid arthritis," Mattey says. "We are trying to make that determination at the moment." **–Ed Susman**

Tracking WTC Exposures

When the World Trade Center collapsed on 11 September 2001, thousands of people were exposed to harmful substances including lead, asbestos, and particulate matter. The ATSDR and the New York City Department of Health and Mental Hygiene have joined forces to create a registry that will identify those people and track their physical and mental health to determine whether the exposures can be linked to any short- or long-term adverse health effects. FEMA is providing $20 million to establish the registry, which is scheduled to begin collecting data in late 2002 or early 2003. Officials hope to have the initial data compiled by the end of 2003.



Global Rules for GM Foods

Members of the Codex International Task Force on Foods Derived from Biotechnology agreed at their March 2002 meeting that genetically modified foods should be subject to premarket safety assessments on a case-by-case basis, and that nations should be allowed to trace such foods as part of their risk management strategies. Tracing systems give regulators the ability to withdraw such products from the market if they are later found to cause adverse health effects. The agreement bolsters efforts by the European Union to introduce tracing systems and will be submitted for adoption to the Codex Alimentarius Commission at its July 2003 meeting. The commission sets voluntary but highly influential international standards for all areas of food production and regulation.

Sequencing *Streptomyces*

In the 9 May 2002 issue of *Nature*, a team of British and Taiwanese scientists announced they had completed sequencing the genome of *Streptomyces coelicolor*. The streptomycetes, common soil bacteria, are used to produce anti-tumor agents, immunosuppressants, and more than two-thirds of all naturally derived antibiotics. The largest bacterial genome sequenced to date with 7,825 genes, *S. coelicolor* is related to the bacteria that cause tuberculosis, leprosy, and diphtheria. Genome data gathered for this project are already being used to help better understand these related bacteria, as well as aid in the development of new drugs to help counter the spread of antibiotic resistance.

Streptomyces coelicolor

Top to bottom: FEMA; ImageBank; ©John Innes Centre

MOLECULAR BIOLOGY

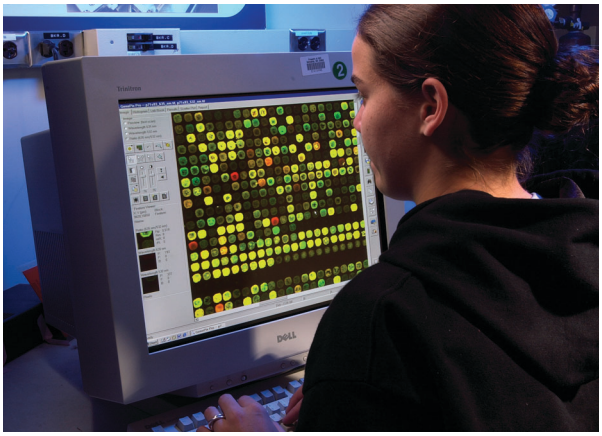
Profiles in Cancer

Historically, pathologists have struggled to distinguish many of the 50-plus sarcoma subtypes, which often look similar under a microscope. Misidentification could hamper treatment—an oncologist who doesn't realize a tumor is aggressive, for example, might treat it too conservatively, allowing it to spread. Now, however, genetic profiling of several of the most common sarcomas—similar to the DNA fingerprinting used to identify criminals—may enable pathologists to accurately diagnose most soft-tissue sarcomas.

Soft-tissue sarcomas are rare; about 8,700 new cases are diagnosed each year. Soft-tissue sarcomas rank among the deadliest cancers, with a five-year survival rate of about 50%. Studies have implicated Agent Orange and other dioxin exposures. Some cases have been associated with therapeutic radiation, others with workplace exposure to vinyl chloride (used, for example, to produce plastics). Most sarcomas, however, have no known cause.

"Because sarcomas are rare, most pathologists don't see many of them," says Matt van de Rijn, an associate professor of pathology at Stanford University School of Medicine. "This [technology] will increase our ability to diagnose sarcomas." Van de Rijn and his colleagues published a study of sarcoma profiling in the 13 April 2002 issue of *The Lancet*. Other researchers are conducting similar sarcoma studies at Memorial Sloan-Kettering Cancer Center, the University of Minnesota, the University of Utah, and several institutions in Europe. At the 38th annual meeting of the American Society of Clinical Oncology in May 2002, the Sloan-Kettering team presented research in which they developed DNA expression profiles that can be used to accurately diagnose nine soft-tissue sarcoma subtypes, representing approximately 70% of these cancers.

To develop such profiles, researchers use a gene-expression microarray, or "gene chip." The chip contains thousands of known gene samples printed onto a quartz wafer in tiny dots. When a gene in a study cell matches one on the chip, it binds tightly, like two pieces of a puzzle. The cellular material causes the matched gene dot to light up. A computer than analyzes the pattern of luminescent genes that make up the cell's profile.



The profiler. Scientists are using microarrays to develop genetic profiles of several common sarcomas in hopes of better diagnoses.

The profiling technique can potentially improve the prognosis for countless patients with more common forms of cancer. "This is a very general technique that will have ramifications for all types of cancer, including the more common ones such as lung, breast, colon, and prostate," says Robert Maki, a medical oncologist and investigator in the Sloan-Kettering work. "All the common cancers are being investigated." Scientists from the National Human Genome Research Institute and Lund University in Sweden reported in the 1 June 2001 issue of *Nature Medicine* that they used genetic profiling to distinguish four childhood cancers that look similar under a microscope: neuroblastoma, rhabdomyosarcoma, non-Hodgkin lymphoma (Burkitt lymphoma), and Ewing sarcoma.

Profiling may eventually help oncologists select the best drugs for treatment. For example, the gene *ERCC1* is associated with resistance to cisplatin, a key drug used in treating ovarian cancer. Oncologists who know that a patient expresses the *ERCC1* gene would choose other drugs. Pharmaceutical researchers also can use this information in drug development to design new chemotherapy drugs that disable drug-resistant genes or target susceptible genes. "If we can identify [genetic] targets," says Maki, "we may be able to develop drugs that attack those targets." **–Cynthia Washam**

GENETIC RESEARCH

Jumpstarting DNA Repair

Every day, your DNA suffers damage—ultraviolet radiation, pollution, and cigarette smoke all take their toll. If unchecked, this damage can produce more extensive DNA lesions that result in tumors. Fortunately, DNA continuously repairs this damage. Now, for the first time, scientists have identified a protein that senses DNA damage from ultraviolet radiation and may trigger the repair process, known as the DNA damage checkpoint system.

A team from the University of North Carolina at Chapel Hill have found that a protein named ATR directly binds to DNA. Their study, published in the 14 May 2002 issue of *Proceedings of the National Academy of Sciences*, adds to scientists' broad knowledge about cancer and how cells protect themselves from DNA damage. "The DNA damage checkpoint system is really what determines cell death or survival, in both normal cells and cancerous cells," says principal investigator Aziz Sancar, a professor of biophysics and biochemistry. "ATR is a key protein in understanding this system."

Scientists already knew that ATR was somehow involved in the damage checkpoint system, but some had speculated that an intermediary protein actually sensed the damage. "We demonstrated that, without an intermediary, ATR binds to DNA, and when there is DNA damage [ATR] binds with higher affinity," says Sancar. "It is the first biochemistry paper showing that this protein has affinity for damaged DNA and can sense the damage directly."

The researchers purified ATR from human connective tissue cells, then mixed the purified ATR with both damaged and undamaged DNA. They then measured the binding using different methods of biochemical analysis as well as electron microscopy. In one method, the researchers bound the ATR to carbohydrate beads, added radiolabeled DNA, washed the beads three times to eliminate unbound DNA, and then visualized the ATR-bound DNA by autoradiograph. Measuring the radioactivity indicated the amount of DNA bound to the ATR. The findings all showed that ATR bound directly to DNA, and bound with twice the affinity to damaged DNA.

The authors call the twofold difference in binding modest, but Jim Drummond, an assistant professor of biology at Indiana University Bloomington who specializes in the mechanisms of DNA repair pathways, says that small differences found during *in vitro* experiments can be significant *in vivo*. "When you look in the cell, those sort of small [DNA-level] differences can be amplified into very large [organism-level] differences," he says.

According to Drummond, the next logical step is to identify the specific sequence of cellular signals that make up the checkpoint system—how ATR's binding to damaged DNA results in a change in the cell cycle and the actual repair of the DNA. Understanding that sequence could eventually provide researchers with clues to possible gene targets for drugs or other therapies. **–Angela Spivey**

Arnold Greenwell/EHP

EHP Toxicogenomics

Toxicogenomics focuses on determining the role that genes play in biological responses to environmental toxicants and stressors. This new scientific discipline has sprung from the dramatic progress being made in numerous genome sequencing projects and the advances taking place in genomic technologies for expression profiling of mRNAs and proteins.

In January 2003, *Environmental Health Perspectives* (*EHP*) will launch a new quarterly edition, *EHP Toxicogenomics*. A complementary website, located at http://ehp.niehs.nih.gov/txg/, brings together vital information being generated in this emerging field. In addition to housing the online version of *EHP Toxicogenomics*, the site will also feature additional scientific resources such as data sets and supplementary materials, to provide the essential information needed to keep up to date in this fast-evolving field.

EHP Toxicogenomics will include the latest original peer-reviewed research from the related disciplines of toxicogenomics, pharmacogenomics, metabolomics, proteomics, and translational aspects of genomic research, as well as commentaries and news articles. The Call for Papers link on the homepage allows visitors to access *EHP*'s instructions for authors and provides an address for electronic submissions.

Readers can also retrieve articles relating to toxicogenomics published in the monthly edition of *EHP* through the Other *EHP* Articles on Toxicogenomics link. This link leads to a list of editorials and news articles published over the past two years, and will be updated as new articles are published.

EHP Toxicogenomics editor Ken Ramos, a molecular toxicologist at Texas A&M University, is introduced on the site, as are the seven associate editors, leading scientists in the fields of computational biology, informatics, genomics, molecular medicine, and proteomics. The site also introduces the 21-member editorial review board, which will oversee the journal's peer-review process.

With its expertise in closely related areas such as toxicology, exposure assessment, and microarray technology, the NIEHS has been at the forefront of toxicogenomics. June 2000 saw the launch of the National Center for Toxicogenomics, which will oversee work at cooperating research institutions through a grants consortium program. Links to the websites for both the center and the grants consortium are posted on the *EHP Toxicogenomics* homepage. **–Erin E. Dooley**

London Trams to Ease Traffic Woes

Traffic-choked areas of central London will receive two public tram routes as part of that city's ongoing efforts to reduce traffic and air pollution. The May 2002 announcement of the routes, which are expected to cost approximately £500 million and transport almost 125 million passengers each year, follows the success of a tram route in London's southern suburbs that opened in May 2000. On that route, 19% of tram riders formerly drove automobiles. Electric-powered trams, which are seeing a renaissance in cities around the world, produce less noise and less air pollution than more conventional modes of transportation.

Six Selected for Sequencing

In May 2002, the National Human Genome Research Institute designated six organisms as the next group to be considered for genome sequencing once capacity becomes available. The chicken, the chimpanzee, several species of fungi, the honeybee, the sea urchin, and the protozoan *Tetrahymena thermophila* were selected based, among other factors, on their importance to medical, biological, and evolutionary studies. By comparing the DNA sequences of a wide variety of organisms to that of humans, scientists hope to find the roots of many human diseases.

Of Mice and Gen

An advanced draft of the mouse genome was made publicly available in early May 2002 by the Mouse Genome Sequencing Consortium, funded in part by the NIH. Comparing the mouse genome to the human genome will allow scientists to identify genetic information that has been preserved across species over hundreds of millions of years and that is therefore functionally important to both species. This, in turn, could lead to the identification of genetic contributors to human illnesses and the discovery of key regulatory elements in the human genome. The project also stimulated the development of two computer algorithms for assembling large genomes, tools that will be extremely useful in looking at the genomes of other species.

Top to bottom: www.croydon-tramlink.co.uk; Matt Turner/EHP; Arnold Greenwell/EHP